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PATENT SPECIFICATION

NO DRAWINGS

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International Classification:—C 07 d 49/38

COMPLETE SPECIFICATION

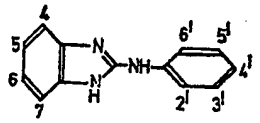
Anilinobenzimidazoles having Antibacterial Properties

We, UNILEVER LIMITED, a Company registered under the laws of Great Britain, of Port Sunlight, in the County of Chester, England, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new anti-bacterial compound and to anti-bacterial compositions containing these compounds.

It has been discovered that 2-anilinobenzimidazoles in which at least two of the carbon atoms in the aromatic rings are substituted with Cl, Br, CF_3 or chlorophenoxy, the substituents being either the same or different, have useful anti-bacterial properties.

Accordingly the invention provides a 2-anilinobenzimidazole in which at least two of the carbon atoms in the aromatic rings are substituted with Cl, Br, or CF_3 or chlorophenoxy. Preferred are those compounds in which at least three of the carbon atoms in the aromatic rings are substituted with Cl, Br, CF_3 or chlorophenoxy. 2-Anilinobenzimidazoles are numbered herein:



Particularly preferred 2-anilinobenzimidazoles are those in which three of the 5, 6, 3' and 4' or 5, 6, 4' and 5' positions are substituted with Cl, Br, CF_3 or chlorophenoxy. Preferred substituents are Cl, Br, and CF_3.

Examples of compounds according to the invention are 5-chloro-2-(3, 4-dichloroanilino) - benzimidazole; 2 - (4 - chloroanilino) - 5, 6 - dichlorobenzimidazole; 5 - chloro - 2 - (3,5 - ditrifluoromethylanilino) - benzimidazole; and 5 - chloro - 2-(3, 4-dibromoanilino)-6-ethylbenzimidazole. Substituents other than Cl, Br, CF_3 or chlorophenoxy that can be present include alkyl, alkoxy, non-halogenated aryloxy, and nitro.

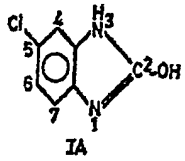
The compounds of the invention can be prepared by heating the appropriate 2-chlorobenzimidazole with the appropriate aniline at high temperature. The product, or its hydrochloride from which the required product can be readily obtained, can be isolated directly from the reaction mixture.

Another method of preparing the compounds of the invention is by the direct halogenation of 2-anilinobenzimidazoles which are readily obtained often in greater than 80% yield, by condensing 2-chlorobenzimidazoles with anilines.

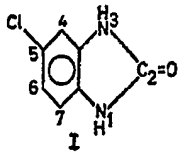
Bromination of 2-anilinobenzimidazole in 80% acetic acid with three equivalents of bromine gives a 33% yield of a pure tribromoderivative.

[1]

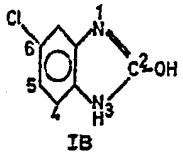
Nomenclature for 2-substituted benzimidazoles



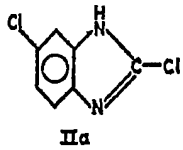
IA



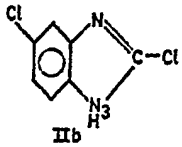
I



IB



IIa



IIb

Compound I above is correctly named 5-chloro-2-benzimidazole. However it can theoretically exist in either of 2 (non-identical) enol forms IA and IB, which if we designate the (—C=N—) nitrogen as the 1-position, are correctly named 5 and 6-chloro-2-hydroxybenzimidazole respectively.

From our present knowledge we must assume that both forms IA and IB are present when any reaction is carried out on 5-chloro-2-benzimidazolone. For example when hydroxyl is replaced by chloro there are two possible products IIA and IIB which are correctly named 2,5-dichloro and 2,6-dichlorobenzimidazole respectively. The product in this reaction is therefore best named 2,(5 or 6)-dichloro benzimidazole. Similar arguments apply to the 2-anilinobenzimidazoles. For example, the product obtained by condensing 2,(5 or 6)-dichlorobenzimidazole and 3,4-dichloroaniline is best named (5 or 6) chloro-2-(3,4-dichloroanilino) benzimidazole. It may well be that in practice a single isomer is formed. However at present we have no means of determining which isomer it is.

A further aspect of the invention is an anti-bacterial composition containing a compound of the invention together with a biologically acceptable carrier.

It has been found that the compounds of the invention are active in detergent compositions and are particularly suitable for incorporation in germicidal and deodorant soaps.

Accordingly one aspect of the invention is a detergent composition containing a bacteriostatically effective amount of a compound of the invention.

A further aspect of the invention is a germicidal or deodorant soap containing a bacteriostatically effective amount of a compound of the invention.

EXAMPLE I

2-(3,4-dichloroanilino)-(5 or 6)-chlorobenzimidazole

2,(5 or 6)-dichlorobenzimidazole was prepared by boiling 15.0 g. 2-hydroxy(5 or 6)-chlorobenzimidazole under reflux for 30 minutes with 150 ml. of phosphorus oxychloride. Hydrogen chloride gas was then passed through the refluxing solution for three hours. The excess phosphorus oxychloride was removed under vacuum and the residue treated with 250 mls. of ice water. The reaction mixture was filtered to give 8.0 gms. of recovered 2-hydroxy-5-chloro-benzimidazole (m.p. 320—325°). The acidic filtrates were neutralised by the addition of ammonia and the precipitated solid was filtered off to give 11.1 gm. (52.5%) of pure 2,(5 or 6)-dichloro-benzimidazole m.p. 193—197° (softens, bubbles, resets).

An intimate mixture of 1.9 gms. (0.01 moles) of 2,(5 or 6)-dichlorobenzimidazole and 1.61 gms. (0.01 moles) of 3,4-dichloroaniline were heated on an oil bath at 180—190°C. for three hours. The cooled crude product mixture was pulverized, washed with several portions hot 2N hydrochloric acid and filtered. The filtered solid was then washed with 2N sodium hydroxide to liberate the free base. There was isolated in this

way 2.0 gms. (64%) of (5 or 6) chloro-2-(3,4-dichloroanilino) benzimidazole m.p. 212—214 from an ethanol water mixture.

The above procedure was repeated using first a two fold then a three fold excess of 3,4-dichloroaniline. No significant improvement in yield was observed.

The minimum inhibitory concentration (in parts per million) to *Staph. aureus* was determined by the tube dilution procedure. The value of 0.8 was obtained.

The germicidal effectiveness of soap containing 2-(3,4-dichloroanilino)-(5 or 6)-chloro-benzimidazole was measured by means of the Finger Imprint Test.

In this test each subject used a 21 cm. square dish containing 37 mls. of nutrient agar seeded with 1 ml. of an overnight culture of *Staph. aureus* in yeast glucose broth.

The fingers of the subject's hands were immersed in small beakers containing 10% soap solution (germicide being present in some beakers at the 1% level based on soap). The subject's fingers were immersed for 30 seconds in the soap solution, rinsed under running tap water for 30 seconds and then dried. The fingertips were then placed in contact with the seeded agar for 2 minutes. The plates were then incubated at 37°C. overnight and the contacted areas examined for absence of bacterial growth. A sharply outlined clear zone is given a rating of 4, a clear area with a hazy periphery is rated at 3, a hazy but acceptable imprint 2, a barely acceptable imprint 1, no detectable imprint 0. A number of subjects were used in each experiment and the average figure taken.

In this test 2-(3,4-dichloroanilino)-(5 or 6)-chlorobenzimidazole gave a rating of 2.

Examples of compounds according to the invention were prepared as follows. Analysis results & MIC (minimum inhibitory concentrations) against *Staph. aureus* are given in Table I which also contains, for comparison purposes, results for 2-anilino- and 2-(*p*-chloroanilino)-benzimidazole.

EXAMPLE II

(5 or 6)-chloro-2-(*p*-chloroanilino) benzimidazole

An intimate mixture of 9.30 gms. (0.05 moles) of 2,(5 or 6) dichlorobenzimidazole and 6.25 gms. (0.05 mole) of *p*-chloroaniline were heated at 180—190°C. for three hours. The crude product was pulverized, washed with several portions of hot 4N hydrochloric acid, filtered and dried. The dry blue solid was extracted with hot chloroform until most of the colour had been washed out and the remaining solid then stirred for 15 minutes with warm dilute ammonia solution to ensure conversion to the free base of the product. This gave 5.0 gms. (36%) of (5 or 6) chloro-2-(*p*-chloroanilino)-benzimidazole m.p. 187—189° from an ethanol water mixture.

EXAMPLE III

(5 or 6)-chloro-2-(*m*-chloroanilino) benzimidazole

Using the method described above for (5 or 6) chloro-2-(*p*-chloroanilino) benzimidazole there was prepared 23% of (5 or 6) chloro-2-(*m*-chloroanilino) benzimidazole m.p. 168—170°C. from benzene.

EXAMPLE IV

(5 or 6) chloro-2-(3-chloro-6-*p*-chlorophenoxy anilino) benzimidazole

An intimate mixture of 3.72 gm. (0.02 moles) of 2,(5 or 6) dichloro benzimidazole and 5.06 gms. (0.02 moles) of 4,4'-dichloro-2-amino diphenyl ether was heated at 180—190°C. for three hours. The crude solid was stirred in dilute ammonia solution and the solution then extracted with ether (in which the dichloro compound is insoluble). The dried ether extracts were evaporated and the residue extracted with several portions of 40—60 petroleum ether, to remove unreacted 4,4' - dichloro - 2 - amino diphenyl ether. The insoluble fraction crystallised from an ethanol water mixture to give 2.0 gms. (36.6%) of pure (5 or 6) chloro-2-(3-chloro-6-chloro-phenoxyanilino) benzimidazole m.p. 202—4.

EXAMPLE V

Bromination of 2-anilinobenzimidazole

To a stirred solution of 1.0 gms. (0.005 moles) of 2-anilinobenzimidazole in a mixture of 8.0 mls. of acetic acid and 2.0 mls. of water at 60°C. was added dropwise a solution of bromine in glacial acetic acid of concentration 0.001 moles/ml. Addition was continued until bromine appeared to be in permanent excess (15 mls.) and the reaction mixture then heated and stirred for an additional 30 minutes The reaction mixture was then poured over 50 gms. of crushed ice and the precipitated solid filtered to give 3.1 gms. of a white solid m.p. 180—250°. The filtered solid was then warmed with 2N sodium hydroxide for 30 minutes and the hot solution filtered. There was filtered off in this way 0.7 gms. (33%) of a tribrominated compound, (mass spec. shows M.W.=446, for analysis see Table I) m.p. 261—264° from a benzene-ethanol mixture.

TABLE I

Analytical and Bacteriological Data for 2-Anilinobenzimidazoles

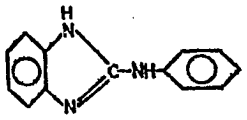
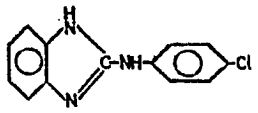
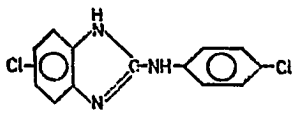
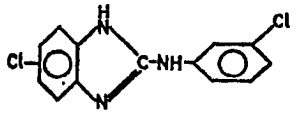
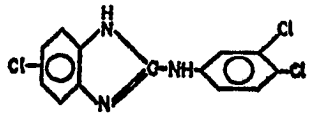
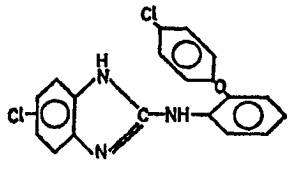
2-anilinobenzimidazole structure	m.p.	% Yield	Calculated				Found				M.I.C. (p.p.m.)
			% C	% H	% N	% Cl	% C	% H	% N	% Cl	
	193—5	83.7	74.6	5.25	20.15	—	74.59	5.77	20.00	—	150
	194—6	71.9	64.10	4.11	17.30	14.6	64.16	4.89	16.95	14.15	50
	182—4	36.0	56.20	3.24	15.11	25.55	55.68	3.45	15.95	25.17	5.0

TABLE I (Continued)

2-anilinobenzimidazole structure	m.p.	% Yield	Calculated				Found				M.I.C.
			% C	% H	% N	% Cl	% C	% H	% N	% Cl	
	168—70	23.0	56.20	3.24	15.11	25.55	56.25	3.33	15.70	24.70	5.0
	212—14	64.0	49.90	2.58	13.40	34.1	50.13	2.49	13.37	33.46	0.8
	202—4	36.6	56.40	2.97	10.40	26.4	55.70	2.80	10.35	25.4	0.5—1
A tribrominated 2-anilinobenzimidazole (Example V)	261—4	33	35.10	1.80	9.44	53.80	35.97	1.80	9.29	53.00	<1.0

WHAT WE CLAIM IS:—

1. A 2-anilinobenzimidazole in which at last two of the carbon atoms in the aromatic rings are substituted with Cl, Br. CF_3 or chlorophenoxy.

2. A 2-anilinobenzimidazole according to Claim 1 in which at least three of the carbon atoms in the aromatic rings are substituted with Cl, Br, CF_3 or chlorophenoxy.

3. A 2-anilinobenzimidazole according to Claim 2, in which three of the 5,6,3′ and 4′ or 5, 6, 4′ and 5′ positions as defined herein are substituted with Cl, Br, CF_3 or chlorophenoxy.

4. A 2-anilinobenzimidazole according to any one of claims 1 to 3 in which C, Br or CF_3 are the substituents in the aromatic rings.

5. A 2-anilinobenzimidazole according to any one of Claims 1 to 3 in which a chlorophenoxy group is the substituent in the aromatic rings.

6. (5 or 6)-chloro-2-(3,4-dichloroanilino)-benzimidazole.

7. (5 or 6)-chloro-2-(p-chloroanilino)-benzimidazole.

8. (5 or 6)-chloro-2-(m-chloroanilino)-benzimidazole.

9. (5 or 6)-chloro-2-(3-chloro-6-p-chlorophenoxyanilino)-benzimidazole.

10. A process for preparing a 2-anilinobenzimidazole according to any one of Claims 1 to 9, in which a 2-chlorobenzimidazole is condensed with an aniline.

11. A process for preparing a 2-anilinobenzimidazole according to any one of claims 1, 2, 3 and 4, in which a 2-anilinobenzimidazole having at least three of the carbon atoms in the aromatic rings unsubstituted is halogenated.

12. A process according to Claim 11, in which the 2-anilinobenzimidazole having at least three of the carbon atoms in the aromatic rings unsubstituted is brominated.

13. A process for preparing a 2-anilinobenzimidazole according to Claim 1 according to any one of the Examples.

14. A bacteriostatic composition comprising a 2-anilinobenzimidazole according to any one of Claims 1 to 9 and a biologically acceptable carrier.

15. A bacteriostatic composition comprising a 2-anilinobenzimidazole prepared by a process according to any one of Claims 10 to 13 and a biologically acceptable carrier.

16. A detergent composition comprising a bacteriostatically effective amount of a 2-anilinobenzimidazole according to any one of Claims 1 to 9.

17. A detergent composition comprising a bacteriostatically effective amount of a 2-anilinobenzimidazole prepared by a process according to any one of Claims 10 to 13.

18. A detergent composition according ao Claim 16 or 17 in the form of a toilet bar.

J. M. REID,
Agent for the Applicants.

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